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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/517,881	06/29/2005	Robin Mark Bannister	GJE.7147	1605

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EXAMINER	
JAVANMARD, SAHAR	
ART UNIT	PAPER NUMBER
1617	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/517,881	BANNISTER ET AL.	
	Examiner	Art Unit	
	SAHAR JAVANMARD	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 April 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4-6 and 8-14* is/are pending in the application.

4a) Of the above claim(s) *12* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 4-6, 8-11 and 13-14* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *04/28/09*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of the Application

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on April 28, 2009 has been entered.

This Office Action is in response to Applicant's arguments filed on April 28, 2009. Claim(s) 1, 4-6, and 8-14 are pending. Claims 2-3 and 7 are cancelled. Claim(s) 11 has been amended. Newly submitted claim 12 is directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: The specification only discloses an in vivo study whereby nefopam is administered prior to morphine administration. There is no support for a study whereby the cause of nausea is anything but morphine.

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claim 12 withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

Claim(s) 1, 4-6, 8-11 and 13-14 are examined herein.

Response to Arguments

Applicant's arguments with respect to the 103(a) rejection of claims 1, 5, and 11 as being unpatentable over Mimoz et al. (*Anaesthesia*, 2001) and McLintock et al. (*British Journal of Surgery*, 1988) in view of Mather et al. (*Chirality*, 2000) have been fully considered but are not persuasive.

Applicant's arguments with respect to the 103(a) rejection of claims 4, 6, 8-10 are rejected as being unpatentable over Mimoz et al. (*Anaesthesia*, 2001) and McLintock et al. (*British Journal of Surgery*, 1988) in view of Mather (*Chirality*, 2000) as applied to claims 1, 5, and 11 above in further view of Sridhar (Cancer, 1988) have been fully considered but are not persuasive.

Applicant continues to argue that the teachings of Mimoz suggest that "any reduction in nausea or vomiting is the consequence of a reduced dosage of morphine." Examiner respectfully notes that Mimoz teaches that the decreased risk of nausea upon extubation may have resulted from the administration of nefopam. Although Mimoz does not specifically employ the term "antiemetic", it is obvious that in fact nefopam does play a role, be it additive with morphine, in decreasing nausea. Furthermore, McLintock specifically compares morphine with nefopam and morphine with a placebo in order to assess the morphine-sparing effects of nefopam (see office action mailed on 7/25/07 and 04/28/08). Indeed it is apparent that nefopam plays a role in reducing nausea, thereby effectively playing the role of an antiemetic.

Applicant has provided references that teach that nefopam as an anti-emetic agent. The references have been considered but are not persuasive. Just as there is literature that shows nausea and vomiting as side effects of nefopam, there is literature, as has been presented in the prosecution of the instant application that teaches the contrary. In this light, Applicant argues that because nefopam has been shown in the literature to have side effects such as nausea and vomiting, that the (+) enantiomer, known to be more active, would be expected to be "pro-emetic". As discussed above and set forth on record, Mimoz and McLintock demonstrate that nefopam has the ability to reduce nausea as a side effect when administered with morphine. Thus it would be obvious to one of ordinary skill in the art to use a pure enantiomer, namely (+)-nefopam, with the expectation that it will demonstrate a more pronounced effect on emesis reduction than the parent enantiomeric mixture. The fact that Maher teaches that (+)-nefopam is significantly more potent than the (-)-nefopam enantiomer, would motivate one of ordinary skill in the art to at least try the effectiveness of nefopam as the pure isomers in the treatment of emesis and conditions related thereto.

Thus the 103(a) rejection is hereby maintained for reasons of record and modified below as a result of Applicant's amendments.

The reason or motivation to modify a reference may often suggest what the inventor has done, but for a different purpose or to solve a different problem. It is not necessary that the prior art suggest the combination to achieve the same advantage or result discovered by applicant. While there must be motivation to make the claimed

invention, there is no requirement that the prior art provide the same reason as the applicant to make the claimed invention. MPEP 2144

In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 5, 11, 13 and 14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mimoz et al. (*Anaesthesia*, 2001) and McLintock et al. (*British Journal of Surgery*, 1988) in view of Mather et al. (*Chirality*, 2000).

Mimoz discloses a post-operative study on the effects of analgesia with morphine alone (an opioid analgesic), or in combination with nefopam (abstract).

Mimoz teaches that patients underwent abdominal surgery and were monitored on their recovery based on several factors, one of which was nausea. The patients were administered morphine for the pain (page 520, column line 1-5). The reference further teaches that administration of morphine may be associated with various side-effects, including nausea (page 523, column 1, lines 14-16).

Additionally, Mimoz teaches that patients on the combination therapy had a greater sense of analgesia and a reduced sense of nausea as compared to morphine alone (page 524, column 2, lines 1-19).

Mimoz teaches that nefopam, when given in combination with morphine, reduces nausea and demonstrates a significant morphine-sparing effect (page 524, column 2, lines 10-13). Additionally, Mimoz teaches that other adverse side effects, such as dizziness, are reduced when morphine is administered with nefopam (page 523, table 4).

Similarly, McLintock discloses a post-operative upper abdominal study whereby patients were given morphine with nefopam and morphine with a placebo in order to assess the morphine-sparing effects of nefopam. McLintock teaches that in addition to significant analgesic effects (abstract), the frequency of side-effects (ie, nausea and vomiting) is reduced when nefopam is given in comparision to placebo (page 780, table 4).

Thus McLintock also teaches that when nefopam is given in combination with morphine, nausea is reduced thereby acting as an anti-emetic agent.

Mimoz and McLintock do not specifically teach the use of the pure (+)-nefopam enantiomer.

Mather teaches that the (+)-nefopam enantiomer is 7-30 times more potent than the (-)-nefopam enantiomer.

It would have been obvious to one of ordinary skill in the art at the time of the invention to have employed the drug nefopam to reduce the side effect of nausea post-operatively as taught by Mimoz and McLintock and used the (+)-nefopam enantiomer. The motivation to employ the (+) enantiomer, provided by Mather, teaches that the (+)-nefopam enantiomer is 7-30 times more potent than the (-)-nefopam enantiomer. Thus it is obvious to one of ordinary skill in the art to use the most potent enantiomer available in order to get the maximum effect and the least dosage possible.

Furthermore, the expectation with regard to enantiomers is that activities as they pertain to living systems are expected to be different. *In re Adamson*, 275 F.2d 952, 125 PS.P.Q. 233 (C.C.P.A. 1960). The fundamentals of optical activity and stereoisomerism are well known to persons having ordinary skill in the art. A person having ordinary skill in the art would have known how to resolve the racemic mixture and would have been motivated to do so with the reasonable expectation of achieving enantiomers having substantially different pharmacological activity. It appears as though applicant has determined experimentally what a person of ordinary skill in the art would have expected, namely, that the racemic mixture of the prior art may be

separate (+) and (-) enantiomers possessing substantial different pharmacological activity. This is an expected result. It is well established that expected beneficial results are evidence of obviousness of a claimed invention just as unexpected beneficial results are evidence of unobviousness. *In re Skoll*, 523 F. 2d 1392, 187 U.S.P.Q. 481 (C.C.P.A. 1975); *In re Skoner*, 517 F. 2d 947, 186 U.S.P.Q. 80 (C.C.P.A. 1975); *In re Gershon*, 372 F. 2d 535, 152 U.S.P.Q. 602 (C.C.P.A. 1967);

Claims 4, 6, 8-10 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mimoz et al. (*Anaesthesia*, 2001) and McLintock et al. (*British Journal of Surgery*, 1988) in view of Mather (*Chirality*, 2000) as applied to claims 1, 5, and 11 above in further view of Sridhar (Cancer, 1988) .

Mimoz, McLintock, and Mather are discussed above.

The instant references do not teach the use of (+)-nefopam as an anti-emetic agent induced by chemotherapy. Further said references do not teach the administration of a second agent with anti-emetic properties from the classes of agents as recited in claim 9 and the specific agents in claim 10.

Although it is common knowledge that one of the common side effects of chemotherapy is emesis, Sridhar teaches that this debilitating side effect is the major cause of cessation of effective cancer chemotherapy in some patients. Furthermore, Sridhar teaches that nausea and vomiting can be potentially fatal toxicities in those patients with curable diseases who refuse therapy (page 1508, column I, lines 12-16).

Furthermore, Sridhar teaches that nausea and vomiting occur in a majority of patients receiving cisplatin chemotherapy despite prophylactic single agent anti-emetic therapy. The reference teaches that the combination of three potent anti-emetics, metoclopramide, diphenhydramine, droperidol, and dexamethasone was highly efficacious in preventing nausea and vomiting in moderate or high-dose cisplatin chemotherapy with little toxicity (abstract).

Sridhar teaches that it may be essential to combine anti-emetics which differ in their ability to block the emetogenecity of chemotherapeutic agents at various trigger zones to produce a synergistic or additive effect (pg 1513, column II, lines 5-9).

It would have been obvious to one having ordinary skill in the art at the time the invention was made to have employed (+)-nefopam as an anti-emetic as taught by Mimoz, McLintock and Mather and used it to treat chemotherapy as taught by Sridhar in addition to any other condition that induces emesis, including motion sickness. The motivation would have been to attenuate the commonly known side effects of chemotherapy (ie., nausea and vomiting) or other conditions, increase the quality of life, and decrease the risk of patient non-compliance.

Further, It would have been obvious to one having ordinary skill in the art at the time the invention was made to have used (+)-nefopam as an agent with anti-emetic properties as taught in Mimoz, McLintock and Mather in combination with one or multiple anti-emetic agents as a combination therapy as taught in Sridhar as a method of treating emesis. Generally, "it is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to

form a third composition to be used for the very same purpose ....[T]he idea of combining them flows logically from their having been individually taught in the prior art.', *In re Kerkhoven*, 626 F.2d 846, 850,205 USPQ 1069, 1072 (CCPA 1980).

Conclusion

Claims 1, 4-6, 8-11 and 13-14 are not allowed.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SAHAR JAVANMARD whose telephone number is (571) 270-3280. The examiner can normally be reached on 8 AM-5 PM MON-FRI (EST).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan can be reached on (571) 272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

/S. J./

Examiner, Art Unit 1617

/SREENI PADMANABHAN/

Supervisory Patent Examiner, Art Unit 1617